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ORIGINAL REPORT

Pretreatment CA-125 and Risk of Relapse in Advanced Ovarian Cancer

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ABSTRACT

Purpose
A previous report suggested the nadir serum CA-125 level within the group of patients with ovarian cancer who achieved normalization of CA-125 accurately defined the risk of relapse. Using similar CA-125 subgroups, we sought to determine if the baseline CA-125 level before initiation of maintenance chemotherapy in women achieving a clinically-defined complete response to primary chemotherapy would be of prognostic value.

Patients and Methods
Patients included in this retrospective analysis had been treated on one of two previously reported trials of maintenance chemotherapy (three *v* 12-monthly cycles of paclitaxel; oral altretamine), with a baseline CA-125 level of ≤ 35 u/mL. Progression-free survival (PFS) from study entry was analyzed by the Cox regression model.

Results
The distribution of premaintenance baseline CA-125 levels for the 384 patients was 58%, 34%, and 8% for values of (A) ≤ 10 u/mL, (B) 11 to 20 u/mL, and (C) 21 to 35 u/mL, respectively. The baseline CA-125 was highly statistically significant, either as a categoric variable ($P < .001$) or as a continuous variable ($P < .0001$). Median PFS was 24 months, 17 months, and 7 months for groups (A), (B), and (C), respectively. There was no evidence the CA-125 effect differed by trial or treatment in an interaction analysis ($P = .70$).

Conclusion
The baseline CA-125 level before initiation of maintenance chemotherapy strongly predicts the risk of subsequent relapse. Patients with premaintenance baseline CA-125 values ≤ 10 u/mL have a superior PFS compared with higher levels in the normal CA-125 range.

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INTRODUCTION

Despite the high objective response rate of advanced ovarian cancer to platinum-taxane–based chemotherapy, the large majority of patients ultimately experience relapse of the malignancy.[1-3] As a result, there has been considerable interest in the gynecologic cancer research community in developing a maintenance or consolidation treatment approach that would favorably impact survival, while maintaining an acceptable quality of life during the extended treatment program.[4-8]

In an effort to examine the potential clinical utility of a maintenance strategy, the Southwest Oncology Group (SWOG) conducted a feasibility trial of altretamine administered for 6 months in women in complete clinical remission, following front-line chemotherapy that demonstrated acceptable compliance and a 2-year survival rate from the time of registration of 75%.[7,8] Subsequently, SWOG and the Gynecologic Oncology Group (GOG) conducted a randomized phase III trial, which demonstrated that 12-monthly treatments with single agent paclitaxel, following the attainment of a clinically-defined complete response in advanced ovarian cancer, reduced the risk of relapse by approximately 50% compared with a regimen of three additional monthly treatments.[9] At the time of publication of this manuscript, data regarding the impact of this approach on overall survival were not available but will be subsequently reported with adequate follow-up of the treated patient populations.

A highly provocative report has suggested it may be possible to more adequately define the risk of ultimate relapse in patients with advanced ovarian cancer who achieve a major response to primary chemotherapy, including achieving normalization (≤ 35 u/mL) of their serum CA-125 antigen level, by dividing such patients into three discrete subgroups,

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Table 1. Patient Characteristics (N = 384)

Characteristic	%
Study	
SWOG 9701/GOG 178	75%
SWOG 9386	25%
Tumor grade, n = 359	
1	6%
2	31%
3	64%
Disease stage	
Optimal stage II	65%
Suboptimal III	25%
Stage IV	10%
Tumor histology, n = 380	
Papillary serous	67%
Endometrioid	14%
Undifferentiated	7%
Clear cell	4%
Mixed	3%
Other	5%
Age, years	
< 65	68%
> 65	32%

Abbreviation: SWOG, Southwestern Oncology Group.

based on their nadir serum CA-125 antigen levels (≤ 10 u/mL, 11 to 20 u/mL, > 21 to 30 u/mL).[10]

These data led us to retrospectively assess the impact of similar premaintenance therapy baseline CA-125 groupings (≤ 10 u/mL, 11 to 20 u/mL, 21 to 35 u/mL) on the subsequent risk of relapse in patients who had participated in one of two previously reported trials of maintenance treatment, following the attainment of a clinically-defined complete response to primary chemotherapy.[7-9]

The aim of this exercise was to determine if it would be possible to employ this factor to help better define the patient population who may benefit from a maintenance treatment strategy. We report here the results of this analysis.

PATIENTS AND METHODS

Patient Populations

The details of the two maintenance chemotherapy studies included in this assessment have previously been published,[7-9] and are briefly outlined below.

The SWOG conducted a phase II trial of single-agent altretamine (260 mg/m^2/d orally for 14 days every 28 days for six cycles) in women with

Table 2. Serum CA-125 Distribution by Treatment

Study	Treatment	Study Entry Serum CA-125 Antigen Level ≤10 (%)	< 10-20 (%)	< 20-35 (%)	N
S9701/GOG178	Paclitaxel x 3	57	33	10	143
S9701/GOG178	Paclitaxel x 12	59	35	6	144
S9326	Altretamine	56	36	8	97
Total		58	34	8	384

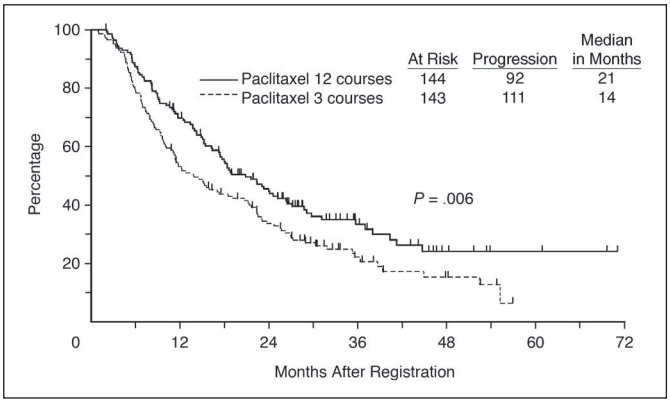

Fig 1. S9701/GOG 178 (three v[r] 12 cycles of monthly paclitaxel) progression-free survival.

stage III advanced ovarian cancer, who had achieved a clinically-defined complete response to primary chemotherapy, which included a premaintenance baseline serum CA-125 antigen level of ≤ 35 u/mL obtained within 42 days before study entry (S9326).[7,8] Patients were then followed until disease progression.

The SWOG and GOG subsequently conducted the previously noted randomized phase III trial comparing single agent paclitaxel (175 mg/m^2 over 3 hours), administered for either 12-monthly or 3-monthly cycles (S9701/GOG178).[9] Patients with both stages III and IV ovarian cancer, who achieved a clinically-defined complete response, were eligible for entry into this trial. A premaintenance therapy baseline serum CA-125 antigen level of ≤ 35 u/mL obtained within 28 days before study entry was required.

Disease progression in S9326 included standard clinical criteria (eg, development of new tumor masses, increase in the size of existing masses), but not changes in the serum CA-125 antigen level, while the definition of disease progression in S9701/GOG178 included both standard clinical criteria as well as an elevation in the serum CA-125 levels to ≥ 70 u/mL, measured on two occasions at least 1 week apart.

Statistical Methodology

A Cox model analysis for progression-free survival (PFS) was employed to assess differences in outcome on the basis of the baseline serum CA-125 antigen levels obtained before study entry. Baseline CA-125 was examined both as categorized by Crawford et al[10,11] (ie, ≤ 10 u/mL *v* 11 to 20 u/mL *v* 21 to 35 u/mL), and as a continuous variable. Research patients were stratified by study and treatment (ie, S9701 paclitaxel- three cycles, S9701 paclitxel-12 cycles, and S9326). Other independent variables included in the Cox regression

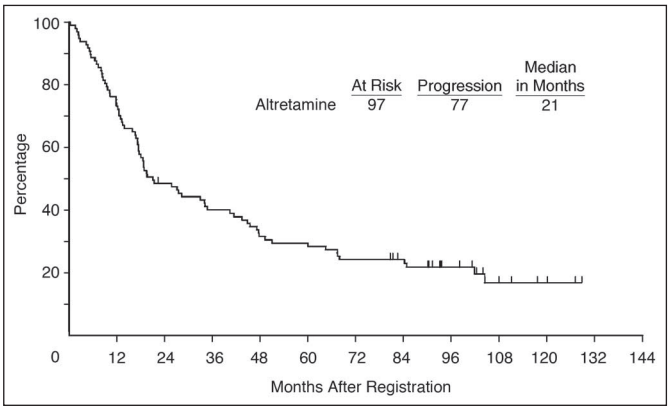

Fig 2. S9326 (oral altretamine for six cycles) progression-free survival.

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Table 3. Progression-Free Survival Event Counts

Study	Treatment	No. of Patients	PFS Events
S9701/GOG178	Paclitaxel x 3	143	111
S9701/GOG178	Paclitaxel x 12	144	92
S9326	Altretamine	97	77

Abbreviation: PFS, progression-free survival.

were disease stage (optimal stage III versus suboptimal stages III or IV), and age (≤ 65 *v* > 65).

To assess the potential differential effects of baseline CA-125 among the three treatment groups, a treatment versus CA-125 interaction analysis was also performed. To assess this interaction, the Cox model included the treatment group indicator variables instead of stratifying by study and treatment. In addition, CA-125 treatment versus CA-125 interaction terms, disease stage, and age were also included in the model. Because of the small number of patients with CA-125 greater than 20 u/mL (ie, a total of 31 among 384 patients), CA-125 was treated as a two-category variable ($\leq$ 10 u/mL *v* $>$ 10 u/mL) in this analysis.

All *P* values presented are two-sided.

RESULTS

Characteristics of the patient population included in this analysis, and distribution of premaintenance therapy baseline CA-125 levels are outlined in Tables 1 and 2, respectively. Figures 1 and 2 demonstrate the PFS for patients treated on S9701/GOG178 (paclitaxel), and S9326 (altretamine), respectively, with the number of PFS events for each protocol outlined in Table 3.

Figures 3 to 6 show the PFS, on the basis of the entry CA-125 levels of all patients and those treated with three cycles of paclitaxel, 12 cycles of paclitaxel, and six cycles of altretamine, respectively.

The Cox model, stratified by study and treatment, revealed a statistically significant impact on PFS for both the amount of residual tumor at the start of primary chemotherapy and the baseline CA-125 level obtained before initiation of the maintenance regimen (Table 4). Median PFS was 24 months (95% CI, 19 to 31 months), 17 months (95% CI, 13 to 18 months), and 7 months (95% CI, 5 to 22 months) in patients with baseline CA-125 values of $\leq$ 10 u/mL, 11 to 20 u/mL, and 21 to 35 u/mL, respectively.

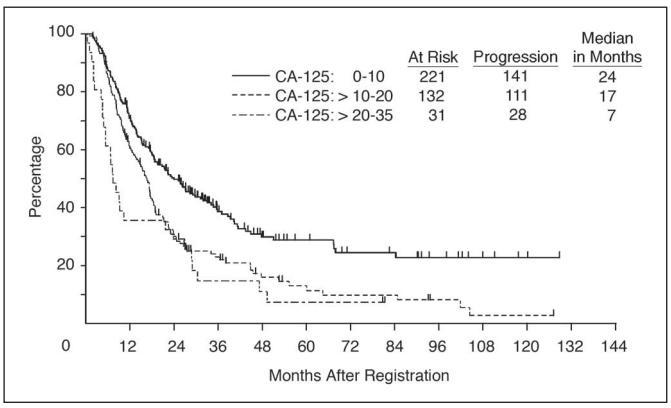

Fig 3. Progression-free survival (all patients) on the basis of entry CA-125 levels.

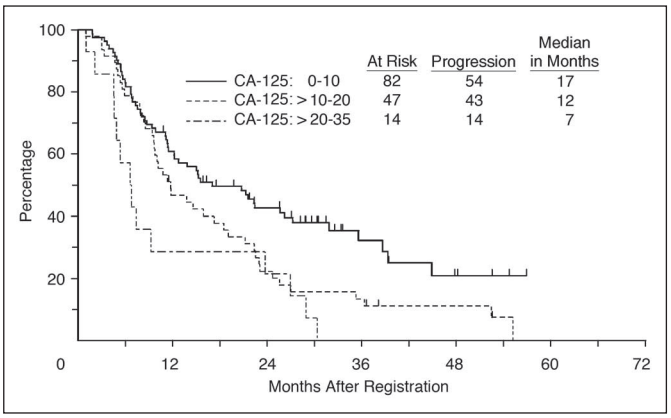

Fig 4. Progression-free survival (S9702/GOG178, paclitaxel x three cycles) on the basis of entry CA-125 levels.

The premaintenance baseline CA-125 level was highly statistically significant either as a categoric variable (χ^2 $P < .0001$ with 2 df), or as a continuous variable ($P < .0001$). The results were similar when tumor histology and grade were added to the Cox regression model. Further, the treatment versus CA-125 interaction analysis showed no indication of inconsistency in the predictive ability of baseline CA-125 across the three treatment regimens investigated ($P = .70$).

In an exploratory analysis, the CA-125 levels of $\leq$ 10 u/mL group was further divided into those $\leq$ 5 u/mL (n = 39) versus those $>$ 5 u/mL but $\leq$ 10 u/mL (n = 182). There were no differences in PFS between these two groups ($P = .99$). This result will need further validation because of its exploratory nature and the small number of patients in the $\leq$ 5 u/mL group.

In S9701/GOG178, the observed differences in median PFS between the 12-monthly cycle and 3-monthly cycle paclitaxel regimens were 9 months (26 months *v* 17 months), 4 months (16 months *v* 12 months), and 0 months (7 months in both groups) in patients with premaintenance therapy baseline CA-125 levels of $\leq$ 10 u/mL, 11 to 20 u/mL, and 21 to 35 u/mL (Figs 4 and 5).

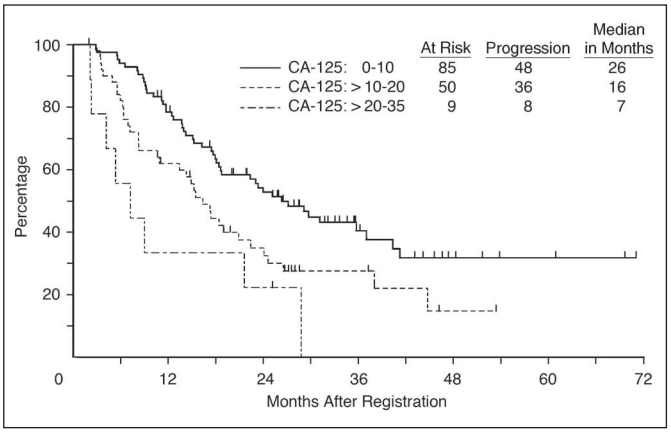

Fig 5. Progression-free survival (S9701/GOG178, paclitaxel x 12 cycles) on the basis of entry CA-125 levels.

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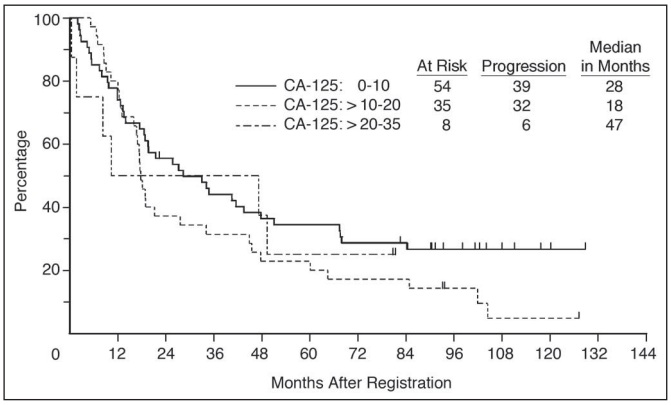

Fig 6. Progression-free survival (S9326) on the basis of entry CA-125 levels.

Table 4. Progression-Free Survival Analysis Cox Model Stratified by Study/Treatment

Variable	Hazard Ratio	*P*
Stage		
Suboptimal stages III or IV versus optimal stage III	1.75	< .0001
Age, years		
< 65 *v* ≤ 65	0.95	.69
CA-125		
< 10-20 *v* ≤ 10	1.51	.002
< 20-35 *v* < 10-20	1.54	.05
< 20-35 *v* ≤ 10	2.32	< .0001

DISCUSSION

Crawford et al[11] observed that survival for one series of ovarian cancer patients receiving chemotherapy varied between groups that attained nadir CA-125 ≤ 10 u/mL (best) *v* 11 to 20 u/mL *v* 21 to 30 u/mL (worst). In their subsequent examination of patients (n = 556) treated with front-line chemotherapy consisting of either carboplatin/paclitaxel or carboplatin/docetaxel (SCOTROC trial), the authors validated this observation and found that women responding to treatment and whose nadir serum CA-125 antigen level was ≤ 10 u/mL experienced a median PFS of 17 months compared with 13 months if the nadir CA-125 was 11 to 20 u/mL and only 8 months with a nadir CA-125 of > 20 u/mL.[10]

In the current analysis, using similar serum CA-125 groups as employed in the Crawford study, we have shown that the baseline antigen level obtained at the time of initiation of maintenance chemotherapy in women with advanced ovarian cancer, who attained a clinically-defined complete response (which included a CA-125 level ≤ 35 u/mL) to primary chemotherapy, is a significant prognostic factor for subsequent disease relapse. Further, the overall impact of this clinical feature was not affected by the specific maintenance regimen administered. (It is likely the one exception to this finding, the prolonged median PFS observed in women with baseline CA-125 antigen levels of 21 to 35 u/mL who received maintenance altretamine, was because of small patient numbers [n = 8] in this sub-group.)

What are the potential clinical implications of these findings? First, the similar results found in patients treated with three different maintenance chemotherapy programs (3-monthly and 12-monthly cycles of single-agent paclitaxel; six cycles of altretamine) and after the attainment of a major clinical response to carboplatin plus either paclitaxel or docetaxel (with normalization of the serum CA-125 level) suggest that the observation is not unique to a particular treatment program. However, a definitive statement regarding this point is not possible because of relatively small numbers in each individual patient subgroup.

Second, the data suggest that future trials of maintenance therapy in this clinical setting should consider this factor to be certain that randomized treatment assignments are balanced within each subgroup (as was the case in S9701/GOG178).

Third, while the total number of patients in each premaintenance therapy baseline serum CA-125 antigen subgroup in the randomized trial comparing three *v* 12 cycles of monthly paclitaxel is limited and do not permit a definitive statement regarding the impact of this clinical factor on the outcome of maintenance therapy, it is of potential interest that the subgroup with the greatest difference in median PFS (9 months) was the group with patients with the lowest baseline CA-125 antigen levels (≤ 10 u/mL). Again, while it is possible this finding is solely because of the problem of small numbers, it is reasonable to speculate this provocative outcome may result from the extended paclitaxel treatment being most effective in patients with: (A) the smallest volume of residual cancer; or (B) the most chemo-sensitive tumors; or (C) a combination of these two factors. Hopefully, future clinical trials will be able to either confirm or refute this hypothesis.

Finally, perhaps the major difficulty faced by clinicians considering maintenance chemotherapy in patients with ovarian cancer, who have achieved a clinically-defined complete response to primary chemotherapy, is the determination of the therapeutic ratio of possible harm versus potential benefit for an individual patient. It will be important for future trials of maintenance treatment in ovarian cancer to carefully assess a role for the premaintenance therapy baseline CA-125 level as one method to help clinicians advise patients in this difficult clinical setting.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Manuscript writing: Maurie Markman, P.Y. Liu, Mace L. Rothenberg, Mark F. Brady, David S. Alberts
Final approval of manuscript: Maurie Markman, Mace L. Rothenberg, Bradley J. Monk, Mark F. Brady, David S. Alberts

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